Reviewer's report

Title: The C allele of the JAK2 rs4495487, an additional candidate locus that contributes to myeloproliferative neoplasm predisposition in the Japanese population

Version: 2 Date: 30 October 2011

Reviewer: Andrea Patriarca

Reviewer's report:

Major Compulsory Revisions

Introduction:

1. The Authors have not cited the study by Olcaydu et al. “The role of the Jak2 GGCC haplotype and the TET2 gene in familial myeloproliferative neoplasms.” Haematologica 2011; 96; 367-74. In this study, performed on familiar MPN, the Authors conclude that, even if the Jak2 46/1 is related to the development of MPN, independently from V617F status, it has to be regarded as only one of the genetic factors involved in the development of MPN;

2. Moreover, recently, Amy V. Jones et al published on Blood 2010 115: 4517-4523 a study performed on patients enrolled in PT-1 trial. In this work the Authors found a correlation in Jak2 wild type MPN between Jak2 46/1 and both MPL exon 10 and Jak2 exon 12. It would be important to cite this work in your introduction.

Materials and Methods:

1. Patients: It is not specified if the clinical data are recorded at diagnosis;

2. Patients: 9 PMF were included into the study. No data on degree of bone marrow fibrosis are provided. It would be interesting to know this variable to try to correlate this data with the presence of the Jak2 haplotype.

3. Statistical Analysis: Only univariate analysis was performed in the present study. It would be correct to perform a multivariable analysis to exclude possible false correlation especially between the molecular biology and clinical data.

Results:

In the section “Clinical and hematological features, JAK2 V617F, and the GCC genotype”:

1. ET

- The Authors found a significant major frequency of splenomegaly in Jak2 wild type ET without the 46/1 haplotype. This result does not agree with those from Vannucchi et al. (Blood 2007; 110: 840) and so it would be helpful to add some speculation in the discussion section.

- About requirement of therapy, the Authors found that Jak2 V617F and
haplotype positive patients required treatment more frequently than Jak2 V617F patients. This finding could be related to a different distribution of age, thrombotic complication and cardiovascular risk factor between the two subgroups. A multivariable analysis could solve this question.

• No difference in platelet count between the different group stratified on molecular biology. This data disagree with our personal data (Patriarca et al. Blood Transfusion 2011) and with Vannucchi et al. Blood 2007. A comment is required in “Discussion”.

2. PV

• The Authors found a major rate of thrombotic complication in PV patients without the GCC genotype, but there is no stratification by cardiovascular risk. It’s possible that the patients without the GCC genotype affected by thrombosis has a worse cardiovascular risk profile which can explain the different complication rate. I think that a multivariable analysis with correction by cardiovascular risk it would be helpful in this field.

• An higher platelet count in PV patients without the genotype is reported. Has a correction by relative iron deficiency been made before analysis? As you know, it’s possible that during PV clone expansion a relative iron deficiency, causing a microcytic appearance of the RBC, could be present. This microcytic appearance could explain this result at least partially.

3. No data are provided on the 9 PMF patients in “Results”.

Minor Essential Revisions
No Minor Essential Revisions has been found.

Discretionary Revisions
Discussion :
In the discussion the Authors cite the study from Colaizzo et al. regarding the frequency of Jak2 46/1 haplotype in splanchnic vein thrombosis. It would be correct, in my opinion, to cite both the work from Smalberg et al. entitled “The JAK2 46/1 haplotype in Budd-Chiari syndrome and portal vein thrombosis” published on Blood 2011; 117: 3968 and that from Kouroupi et al. “The JAK2 46/1 haplotype in splanchnic vein thrombosis” published on Blood 2011; 117: 5777. In this two works the conclusion are in agreement with your data and both the groups conclude that the haplotype is not a risk factor for splanchnic vein thrombosis.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interest